BRUMBAUGH, GRAVES, DONOHUE & RAYMOND
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112-0228

212 408-2500
FACSIMILE 212 765-2519
E-MAIL 6111063@MCIMAIL COM

Appln. Trans.
PATENT

770. / 10

Our File No. 31064 165/36619

Date May 9, 1997

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BY EXPRESS MAIL - LABEL NO. EI357407041US

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Transmitted herewith for filing is the patent application of Inventor(s) full name(s):

STEVEN M. PODOS, THOMAS W. MITTAG and BERNARD BECKER

For: NOVEL PROSTAGLANDINS FOR GLAUCOMA THERAPY

Enclosed are also:

[] Combined Declaration and Power of Attorney.

[] sheets of drawings.

[] An assignment of the invention to

[] is attached. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

[] will follow.

[] A certified copy of a application, No. , filed .

[] Associate Power of Attorney.

[] Verified statement(s) to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27.

[] Other: .

The filing fee has been calculated as shown below:

FOR	(Col. 1) No.Filed		(Col. 2) No. Extra	Small Entity Rate	Fee	OR	Other Than A Small Entity Rate	Fee
Basic Fee					$385			$770
Total Claims	9	-20=	0	x $11=			x $22 =	$0
Ind. Claims	3	-3 =	0	x $40 =			x $80 =	$0
Multiple Dependent Claim				+ 130 =			+$260=	
				Total				$770

* If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

Fee Payment Being Made:

[x] Enclosed

[x] Basic filing fee $770

[X] Recording Assignment [$40.00; 37 CFR 1.21(h)] $ 40.00

Total fees enclosed $770.00

[x] A check in the amount of $770 to cover filing fee is enclosed.

[X] The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16 and/or 37 CFR 1.21(h)(1) associated with this communication or credit any overpayment to Deposit Account No. 02-4377. Two copies of this sheet are enclosed.

BRUMBAUGH, GRAVES, DONOHUE & RAYMOND

By Lisa B Kole
Richard S. Clark
PTO Registration No. 26,154

Lisa B. Kole
PTO Registration No. 35,225

Enclosures

BRUMBAUGH, GRAVES, DONOHUE & RAYMOND
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112-0228

212 408-2500
FACSIMILE 212 765-2519
E-MAIL 61110 63@MCIMAIL.COM

Appln. Trans.
PATENT

Our File No. 31064 165/36619

Date May 9, 1997

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BY EXPRESS MAIL - LABEL NO. EI357407041US

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Transmitted herewith for filing is the patent application of Inventor(s) full name(s):

STEVEN M. PODOS, THOMAS W. MITTAG and BERNARD BECKER

For: NOVEL PROSTAGLANDINS FOR GLAUCOMA THERAPY

Enclosed are also:

[] Combined Declaration and Power of Attorney.

[] sheets of drawings.

[] An assignment of the invention to

[] is attached. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

[] will follow.

[] A certified copy of a application, No. , filed .

[] Associate Power of Attorney.

[] Verified statement(s) to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27.

[] Other: .

The filing fee has been calculated as shown below:

FOR	(Col. 1) No.Filed		(Col. 2) No. Extra	Small Entity Rate	Fee	OR	Other Than A Small Entity Rate	Fee
Basic Fee					$385			$770
Total Claims	9	-20=	0	x $11=			x $22 =	$0
Ind. Claims	3	-3 =	0	x $40 =			x $80 =	$0
Multiple Dependent Claim				+ 130 =			+$260=	
				Total				$770

* If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

Fee Payment Being Made:

[x] Enclosed

[x] Basic filing fee $770

[X] Recording Assignment [$40.00; 37 CFR 1.21(h)] $ 40.00

Total fees enclosed $770.00

[x] A check in the amount of $770 to cover filing fee is enclosed.

[X] The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16 and/or 37 CFR 1.21(h)(1) associated with this communication or credit any overpayment to Deposit Account No. 02-4377. Two copies of this sheet are enclosed.

BRUMBAUGH, GRAVES, DONOHUE & RAYMOND

By Lisa B Kole
Richard S. Clark
PTO Registration No. 26,154

Lisa B. Kole
PTO Registration No. 35,225

Enclosures

FILE NO. 31064 165/36619

BRUMBAUGH, GRAVES, DONOHUE & RAYMOND

30 ROCKEFELLER PLAZA

NEW YORK, NEW YORK 10112

TO ALL WHOM IT MAY CONCERN:

Be it known that WE, STEVEN M. PODOS, THOMAS W. MITTAG and BERNARD BECKER, citizens of U.S.A., U.S.A. and U.S.A. , residing in Tenafly, Pleasantville and University City , County of Bergen, Westchester and St. Louis , State of New Jersey, New York and Missouri whose post office addresses are 2 Knoll Road, Tenafly, New Jersey 07670, 167 Woodland Avenue, Pleasantville, New York 10570 and 8655 West Kingsbury, St. Louis, Missouri 63124 (respectively,) have invented an improvement in

NOVEL PROSTAGLANDINS FOR GLAUCOMA THERAPY

of which the following is a

SPECIFICATION

INTRODUCTION

The present invention relates to the use of 8-iso prostaglandin E_2 ("8-iso PGE_2"), 8-iso prostaglandin E_1, and 8 iso-PGE derivatives in the treatment of glaucoma. It is based, at least in part, on the discovery that 8-iso prostaglandin E_2 effectively decreased intraocular pressure by a trabecular meshwork outflow mechanism.

BACKGROUND OF THE INVENTION

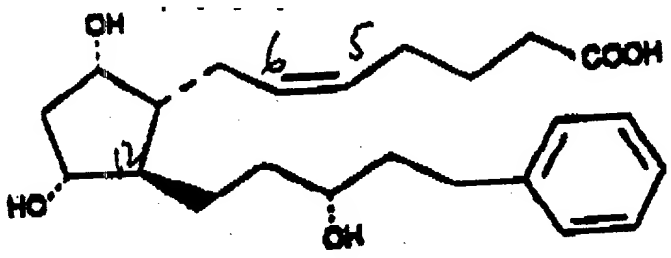
Glaucoma is a major eye disease which can cause progressive loss of vision leading to blindness. The majority of human glaucomas are associated with increased intraocular pressure ("IOP") resulting from an imbalance in the rate of secretion of aqueous humor by the ciliary epithelium into the anterior and posterior chambers of the eye and the rate of aqueous humor outflow from these chambers, primarily via the canal of Schlemm. High IOP is considered the major risk factor for glaucomatous visual impairment resulting from the death of retinal ganglion cells, loss of the nerve fiber layer in the retina, and destruction of the axons of the optic nerve. Current treatments are directed toward reducing intraocular pressure.

Glaucoma is typically classified, on the basis of its etiology, as primary or secondary. Primary glaucoma in adults, a disorder in which the underlying cause is poorly understood, is associated with increased IOP due to an obstruction of aqueous humor outflow . The obstruction may be caused by a blockage located at the angle formed between the iris and the lateral cornea, categorized as either open angle or acute or chronic angle closure. The anterior chamber of the eye appears normal in chronic open angle glaucoma, despite impaired drainage of aqueous humor. In contrast, the anterior chamber is shallow and the filtration angle is narrowed in chronic angle-closure glaucoma, wherein the trabecular network at the entrance of the canal of Schlemm may be obstructed by the iris. An acute attack of glaucoma may arise in this context when the pupil dilates, pushing the root of the iris forward to block the angle.

Secondary glaucoma is caused by another disorder which functionally interferes

with the flow of aqueous humor from the posterior to the anterior chamber. Such interference may be caused by inflammation, a tumor, an enlarged cataract, central retinal vein occlusion, trauma, or hemorrhage.

Several classes of drugs acting by different mechanisms are used as topically administered ocular therapy to lower IOP. These include beta adrenergic blockers (e.g., timolol), topical carbonic anhydrase inhibitors (e.g., dorzolamide), and alpha$_2$ -adrenergic receptor agonists (e.g., clonidine derivatives), all of which act primarily by decreasing the formation of aqueous humor within the eye. Pilocarpine and epinephrine are clinical agents that also lower IOP in glaucomatous eyes, but these drugs act principally by decreasing the resistance in the trabecular meshwork outflow channels. A third mechanism for lowering IOP in the primate eye is by increasing the outflow of aqueous humor via the uveoscleral route. Recently, a prostaglandin derivative belonging to the F2α series of prostanoids, which acts primarily by this uveoscleral mechanism, has been introduced for glaucoma therapy. This drug, called latanoprost, is the isopropyl ester of a compound having the following structure:



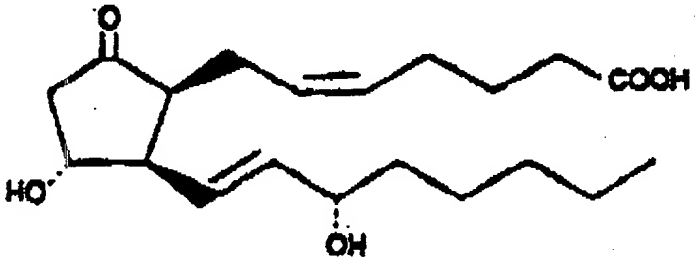
Prostaglandins which may be used in the treatment of glaucoma are described in United States Patents Nos. 5,476,872 by Garst et al., 4,599,353 by Bito, 5,262,437 by Chan,

5,462,968 by Woodward, 4,132,847 by Kuhla, 5,173,507 by DeSantis et al., 5,578,618 by Stjernschantz et al., 5,208,256 by Ueno, 5,565,492 by DeSantis et al., 5,151,444 by Ueno et al., and PCT Application No. PCT/US93/10853, International Publication No. WO 94/11002 by Woodward.

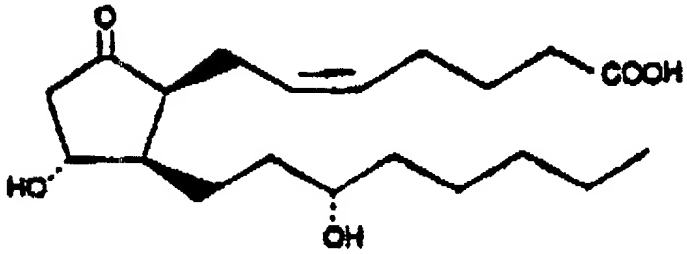
The present invention relates to prostaglandins which are structurally different from latanoprost and other prostaglandins used in the treatment of glaucoma, and that belong to the 8-isoPGE series of prostanoids, for example 8-isoPGE_1 and 8-iso PGE_2. In contrast to latanoprost, 8-isoPGE_2 lowers IOP primarily by decreasing the resistance to trabecular outflow of aqueous humor from the eye.

SUMMARY OF THE INVENTION

The present invention relates to the use of 8-iso prostaglandin E_2 (prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo, (5Z, 8β, 11α, 13E,15S), having the following Formula I:



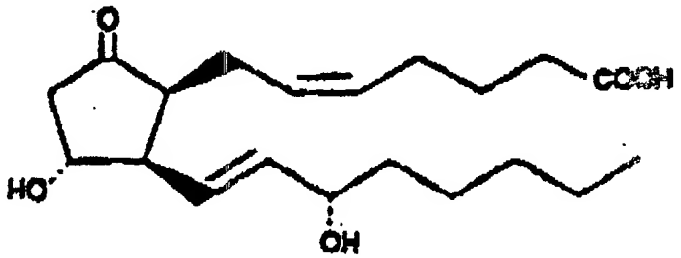
8 iso prostaglandin E_1 having the following Formula II:



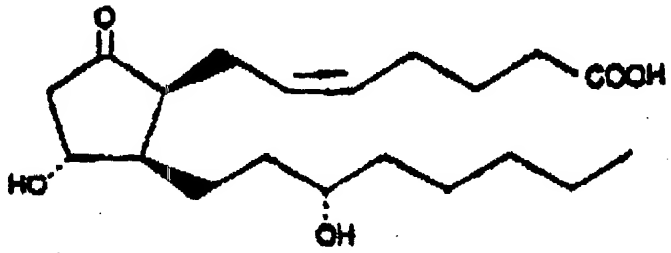
and 8-iso PGE derivatives in the treatment of glaucoma.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of 8-iso prostaglandin E_2 (prosta-5,13-dien-1-oic acid, 11,15-hydroxy-9-oxo, (5Z, 8β, 11α, 13E,15S) ("8-isoPGE$_2$"), having the following Formula I:



8-iso PGE_1, having the following Formula II:



and derivatives of $_8$-isoPGE$_1$ and 8-isoPGE$_2$ in the treatment of increased IOP and/or glaucoma. The main structural differences between 8-isoPGE$_2$ and latanoprost are the following: (i) the side chain substituents on the five-membered rings have the opposite geometric arrangement with respect to the plane of the ring (cis for 8-isoPGE$_2$ and trans for latanoprost); (ii) the five-

membered ring has a keto function at position 9 in 8-isoPGE$_2$, whereas there is a hydroxyl group in the same position in latanoprost; and (iii) the side chains beginning with the twelfth carbon have different structures, with latanoprost containing a terminal phenyl ring. 8 iso-PGE derivatives of the invention contain a five-membered ring and two side chains, and retain distinguishing features (i)-(iii) as set forth in the preceding sentence. In preferred embodiments, such derivatives are esters of 8-isoPGE$_1$ or 8-isoPGE$_2$ For example, esterified derivatives of 8-iPGE$_2$ may be used according to the invention, and may provide improved penetration into the eye.

The mechanism of action by which 8-isoPGE$_2$ lowers IOP has been found to be different from that of latanoprost in experiments done in primates, in that 8-isoPGE$_2$ has been found to increase trabecular outflow facility. This is an advantage in that the trabecular mesh-work is the primary locus of the pathology causing increased IOP in primary open angle glaucoma.

Accordingly, the present invention provides for a method for decreasing IOP, and a method for treating glaucoma, comprising administering a therapeutically effective amount of 8-isoPGE$_1$, or 8-isoPGE$_2$, or a derivative thereof. Suitable formulations include for example, and not by way of limitation, a topical solution which is a physiological saline solution, having a pH between bout 4.5 and 8 and an appropriate buffer system (e.g., acetate buffers, citrate buffers, phosphate buffers, borate buffers) a neutral pH being preferred. The formulation may further comprise a pharmaceutically acceptable preservative (e.g. benzalkonium chloride, thimoserol, chlorobutanol), stabilizer and/or surfactant (e.g. Tween 80). The formulation may also comprise

a compound which acts as a tonicity adjuster (e.g. sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisol, butylated hydroxytoluene). A "therapeutically effective amount" of 8-isoPGE$_1$ or 8-isoPGE$_2$, or a derivative thereof refers to an amount of drug which decreases the IOP by at least about 10 percent, preferably at least about 15 percent, and more preferably at least about 20 percent. In particular embodiments of the invention, the administration of 8-isoPGE$_1$ or 8-isoPGE$_2$, or a derivative thereof results in an increase in trabecular outflow facility of at least about 10 percent, preferably at least about 20 percent, and more preferably at least about 30 percent. In nonlimiting embodiments of the invention, a topical preparation of 8-isoPGE$_1$ or 8-isoPGE$_2$ at a concentration of between .001 and 1 percent, preferably between .005 and .2 percent, and more preferably between about .05 and .1 percent, or equivalent amounts of an 8-isoPGE$_1$ or 8-isoPGE$_2$ derivative (equivalency based on the ability to promote trabecular outflow) may be used.

According to the invention, IOP may be decreased, and/or glaucoma may be treated, using compositions comprising 8-isoPGE$_1$ or 8-isoPGE$_2$, or a derivative thereof, as the sole active agent, or in conjunction with another active agent. For example, combinations of 8-isoPGE$_1$ or 8-isoPGE$_2$, or a derivative thereof, and another drug used to treat elevated intraocular pressure, including but not limited to another prostaglandin derivative (including, but not limited to, latanoprost), pilocarpine, epinephrine, a beta adrenergic agent (e.g., timolol), a carbonic anhydrase inhibitor (e.g., dorzolamide), or an alpha$_2$-adrenergic receptor agonist (e.g., a clonidine derivative), may be used.

EXAMPLE

Experiments were performed to evaluate the effects of single dose administration of 8-isoPGE$_2$ on IOP in normal ("N") and glaucomatous ("G") monkey eyes, and to determine the mechanism by which 8-isoPGE$_2$ alters I0P in N monkey eyes, when applied topically. A single 25µl dose study was performed in 6 N and 8 G monkeys. I0P and pupil sizes were measured before and at 0 hr, 0.5 hr and then hourly for a total of 6 hrs after 0.05% or 0.1% drug concentrations were administered. Tonographic outflow facility ("O") and fluorophotometric aqueous humor flow (F) were determined in 6 N monkeys before and after unilateral application of 25 µl of 0.1% 8-isoPGE$_2$. In 8 G monkey eyes, 8-isoPGE$_2$ reduced IOP ($p<0.005$) up to 2 hrs or 5 hrs following administration of the 0.05% or 0.1% concentration, respectively. The maximum reduction in IOP was 4.6±0.8(mean±SEM)mmMg (0.05%) and 6.6±0.8 mmHg (0.1%), as compared to baseline measurements. After topical application of 8-isoPGE$_2$ the IOP was lower ($p<0.01$) in the treated eyes of 6 N monkeys for 4 hrs, with a maximum difference of 3.2 ± 0.2 mmHg, as compared to the fellow contralateral control eyes. The pupil size was smaller ($p<0.01$) for 4 hrs, up to 1.0 ± 0.2 mm. Compared with vehicle-treated contralateral control eyes, O was greater ($p<0.005$) by 48% at 2 hr after a single dose of 0.1% 8-isoPGE$_2$. F was unexchanged ($p<0.10$) over a period of 4 hrs after drug administration. Mild eyelid edema, conjunctival edema, hypermia, and discharge appeared in some eyes treated with the 0.1% concentration.

Table 1A shows that 8-isoPGE$_2$ administered to the normal monkey eye lowers IOP significantly by 20.3% and increases outflow facility by 43.1%, an amount sufficient to

account for the fall of IOP. By contrast, in Table 1B latanoprost in the normal monkey eye also lowers IOP significantly (by 10.8%), but the drug has no significant effect on outflow facility. The lack of a major effect on outflow facility of latanoprost in the primate eye is in agreement with studies in the literature by other investigators.

Table 1

A. Effect of 0.1% 8-isoPGE$_2$ on Outflow Facility in 6 Normal Monkeys

(2 hours after treatment)

	Intraocular Pressure Mean±SEM mmHg	Outflow Facility Mean±SEM µl/ml/mmHg
Treated eyes (drug)	13.0±0.7*	0.83±0.10*
Baseline	16.3±1.1	0.58±0.03
Control eyes (vehicle)	15.7±0.5	0.56±0.06
Baseline**	15.7±0.6	0.51±0.04

B. Effect of 0.005% latanoprost on Outflow Facility in 6 Normal Monkeys

(1 hour after treatment)

	Intraocular Pressure Mean±SEM mmHg	Outflow Facility Mean±SEM µl/min/mmHg
Treated eyes (drug)	13.2±0.7*	0.76±0.08
Baseline	14.8±0.7	0.62±0.07
Control eyes (vehicle)	15.0±0.8	0.60±0.07
Baseline**	15.7±0.3	0.73±0.08

*Significantly different as compared with either baseline values or vehicle-treated eyes (two-tailed paired t-test, $p.<0.05$.

** Baseline measurements made in the same monkeys at the same time one day prior to drug treatments

Table 2 shows the effect of 8-isoPGE$_2$ on IOP and outflow facility in glaucomatous monkey eyes. Because of the individual variability in laser-induced glaucomatous monkey eyes, the IOP and facility measurements are expressed in the table as ratios (value of the drug-treated eye ÷ the value of the vehicle-treated eye). The ratios were calculated from the values of the same glaucomatous monkey eye determined immediately prior to administration of the drug or the vehicle (time 0 hrs.), and the values at 2 hours after administration of the drug or vehicle. The data in Table 2 show that in the primate, administration of 8-isoPGE$_2$ to glaucomatous eyes significantly lowers IOP (by 13.8%) and significantly increases outflow facility (by 38.8%), which is of sufficient magnitude to account for the fall in IOP. Thus the mechanism of lowering IOP by 8-isoPGE$_2$ in both normal and glaucomatous eyes is primarily due to an increase in aqueous humor trabecular outflow.

Table 2

Effect of 0.1% 8-iPGE$_2$ on IOP and Outflow Facility Responses

in 8 Glaucomatous Monkey Eyes (Unilateral)

	Intraocular Pressure (drug-treated/vehicle-treated)		Outflow Facility (drug-treated/vehicle treated)	
Time	0 hr	2 hr	0 hr	2 hr
response ratio	0.976 ±0.0992+	0.843* ±0.0498	1.041 ±0.154	1.445** ±0.161
%change by drug	—	13.8% decrease	—	38.8% increase

Significantly different as compared to 0 hr, paired t-test, $p<0.01$*, <0.10**

Various publications are cited herein, the contents of which are hereby incorporated by reference in their entireties.

WE CLAIM:

1. A method for decreasing intraocular pressure comprising administering a therapeutically effective amount of 8-isoPGE$_2$ to a patient in need of such treatment.

2. The method of claim 1 wherein the 8-isoPGE$_2$ is administered topically.

3. The method of claim 2 wherein the 8-isoPGE$_2$ is administered as a composition comprising between .005 to 1 percent 8-isoPGE$_2$.

4. A method for decreasing intraocular pressure comprising administering a therapeutically effective amount of a derivative of 8-isoPGE$_2$ to a patient in need of such treatment.

5. The method of claim 4 wherein the derivative is an ester of 8-isoPGE$_2$.

6. The method of claim 4 wherein the derivative of 8-isoPGE$_2$ is administered topically.

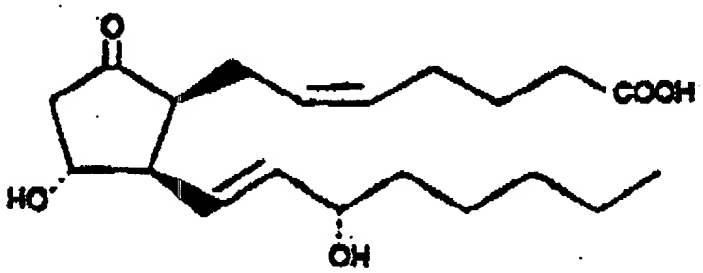
7. A method for decreasing intraocular pressure comprising administering a therapeutically effective amount of8-isoPGE$_1$ or a derivative thereof to a patient in need of such treatment.

8. The method of claim 7wherein the 8-isoPGE$_1$ is administered topically.

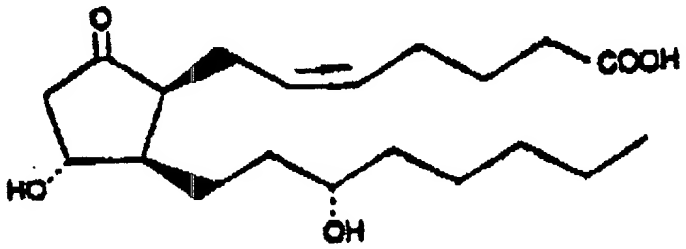
9. The method of claim 8wherein the 8-isoPGE$_1$ is administered as a composition comprising between .005 to 1 percent 8-isoPGE$_1$.

ABSTRACT

The present invention relates to the use of 8-iso prostaglandin E_2 (prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo, (5Z, 8BETA, 11ALPHA, 13E,15S) ("8-isoPGE$_2$") having the following Formula I:



or 8-isoPGE$_1$, having the following Formula II:



and derivatives thereof in the treatment of disorders of increased intrsocular pressure, including but not limited to glaucoma.